Remarks

Claims 1, 3 to 6, 8 to 12, 14 to 21 and 25 to 28 are currently pending in this application of which claims 1, 11, and 25 are in independent form. Amendments to the claims were introduced solely to further clarify the claim language.

Claim Rejections **– 35 U.S.C. §112**

On pages 2 to 3, the Office rejected claims 1, 3 to 6, 8 to 12, 14 to 21 and 25 to 28 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention.

With respect to independent claim 1, the view was expressed that the preamble of the claim did not correspond well with the remainder of the claim.

In response, applicant has amended claim 1 to provide such correspondence.

On page 3, the Office rejected independent claims 11 and 25 as indefinite in view of the phrase "substantial."

As the term substantial was only introduced to clarify the claimed invention for the benefit of the reader applicant has, in response to the Office's rejection, replaced the term substantial with "a."

Also on page 3, the Office continued to reject claims 20, 21 and 28 as indefinite in view of the phrase "a single separation step."

The view was expressed that the claimed method encompassed at least two steps including (a) a step of forming a non-physiological mixture of a blood sample and (b) a step of centrifugation. In the alternative, the view was expressed that a step of "removal" of cellular fraction and subsequent identification of cells within such a fraction does not constitute a "single separation step" as claimed.

Applicant submits that for a claim to be definite it has only to meet "the threshold requirements of clarity and precision." The claims have merely to define the patentable subject matter with a reasonable degree of particularity and distinctness. Definiteness

of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. (MPEP §2173.02).

With regard to the first position taken by the Office, applicant submits that one of the two steps identified by the Office, namely the formation of a mixture, would not be considered a "separation step."

With regard to the second position taken by the Office, applicant submits that claims 20 and 28 are directed towards the isolation of a low density cell fraction in a "single separation step" and not cells. With regard to claim 21, applicant notes the reference to a "separation" device under (b) and (c) of claim 1, which clarifies that the separation takes place in such a "separation" device.

Accordingly, applicant submits that the claim is sufficiently clear to one possessing ordinary level of skill in the pertinent art to meet the threshold requirements of clarity and precision.

New Matter/Written Description

On pages 3 and 4, the Office rejected claims 26 and 27 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

In particular, the view was expressed the limitation "13000 nucleated cells" in claims 26 and 27 has no support in the specification.

In response, applicant respectfully directs the Office's attention to Table 3. This table discloses in column 5, entitled "Nucleated cells analyzed by FISH" certain numbers of nucleated cells that were analyzed. The table also shows in column 7, the "number of cells positive for ε chain Hb." As explained in the paragraph bridging page 10 and 11 of the specification, immunostaining for embryonic hemoglobin and FISH was used to identify fetal NRBCs. Column 5 show that the number of nucleated cells analyzed in 12 samples ranged from 336 (Sample "SCO") to 13767 (Sample "PIN"). Column 7 shows that in each of the 12 samples fetal NRBCs could be detected by

immunostaining for embryonic hemoglobin. Thus, the data supports a claim that not more than 13000 nucleated cells of said low cell density fraction have to be analyzed for reliable non-invasive prenatal investigation. Applicant submits that while newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure, there is no in *haec verba* requirement. Applicant further submits that the written description requirement is in the present case satisfied through sufficient description of a representative number of specific examples (see MPEP §2163). However, in order to address the Office concerns, applicant has amended the claims to recite the exact numbers shown in Table 3.

Enablement

On pages 4 to 7, the Office rejected claim 11, 12, 14 to 21 and 25 to 28 under 35 U.S.C. §112, first paragraph.

In particular, the Office expressed the view that the specification does not provide enablement for a "substantial" separation of NRBCs from lymphocytes and monocytes in blood.

Without conceding the correctness of the Office rejection, applicant has deleted the term "substantial" in front of "separation" from the rejected claims as this term as merely introduced for the benefit of the reader. The usage of the term "separation" in the specification as well as the usage of the term by those skilled in the field of cellular biology as a term of degree. In view of this deletion, this rejection has become moot.

Applicant further notes, that the Office seems to take some issue with the term "non-physiological conditions."

The term "non-physiological" is used in the present context as an umbrella term that includes a wide host of conditions, which, however, are further specified in the claims, either by certain parameters or by their function (In this context, applicant notes that it is well established that there is nothing inherently wrong with defining some part of an invention in functional terms. In re Swinehart, 439 F.2d 210, 169 USPQ 226 (CCPA 1971) (see also MPEP §2173.05(g)). If issue is taken with the term itself, applicant

offers to delete the term wherever it occurs eventhough this might make it hader to follow the claims.

Irrespective and independent of the argument made above, applicant would also like to direct the Office's attention to, for example, United States Patent **6,962,982** (Art Unit 1653; issued November 2005), and the usage of the term "non-physiological" in the specification and claims and in particular claims 1, 10, 18 and 31.

If the Office's concern is one of whether or not a certain condition accomplishes the stated effect, the Office's attention is directed to In re Marzocchi and Horton, 169 USPTO 367 (CCPA 1971) that explains the boundaries of an enablement analysis. In particular, Marzocchi outlines the requirement of objective evidence to support a rejection that is directed at the accuracy of applicant's statements. Id. at 370.

The Office argues that undue experimentation would be required to practice the invention. Factors to be considered in an analysis of whether or not experimentation is undue include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor;(G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Applicant notes that the relative skill of those in fields such as chemistry has been established by the United States Court of Appeals for the Federal Circuit (Federal Circuit) as quite "high" Durel Corp. v. Osram Sylvania Inc., 52 U.S.P.Q.2d 1418, 1433-34 (D.Ariz. 1998) (finding that a person of ordinary skill in the art would be "a junior faculty member with one or two years of relevant experience or a postdoctoral student with several years of experience"). The quantity of experimentation can be considerable and time-consuming as long as the experimentation is merely "routine." For example, experimentation requiring only routine optimization or screening has not been held to be undue experimentation. Wands, 858 F.2d at 736-37. Applicant discloses in his specification that different cell types, in particular hard to separate monocytes/lymphocytes and

NRBCs, respectively, change their densities in different ways, namely one cell type becomes heavier and other becomes lighter when exposed to certain conditions, thus allowing their separation into different cell fractions. Applicant submits that providing this concept by itself, but certainly in combination with the working example provided, would have allowed the person skilled in the art, at the time the invention was made, to vary conditions by routine experimentation and thus to practice the entire scope of the invention as claimed.

On pages 7 to 13, the Office continues to reject claims 1, 3-5, and 8 under 35 U.S.C. §103(a) as well as claims 10 to 12, 14 to 21 and 25 to 28 as being unpatentable over U.S. Patent No. 5,641,628 to Bianchi (hereinafter "Bianchi") in view of U.S. Patent No. 5,676,849 to Sammons et al. (hereinafter "Sammons"), U.S. Patent No. 5,432,054 to Saunders et al. (hereinafter "Saunders") and Guyton's Textbook of Medical Physiology.

Applicant submits that to establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations (MPEP §2142).

Applicant notes that with regard to all rejected claims, but in particular with regard to claims 6, 9, 26 and 27 an indication where such a teaching or suggestion of the claim limitations added by those claims can be found is lacking.

Applicant has argued this rejection previously in the response filed on June 30, 2004 and the response filed on June 24, 2005. Rather than repeating the arguments already made and to which the Office is respectfully directed, applicant would like to focus in this response on selected limitations of the rejected claims:
Claims 11 and 25 require:

> *"causing the density of said NRBCs to decrease and the cell density of said monocytes and lymphocytes to increase . . . "*

None of the references cited by the Office discloses such a step. Rather, it appears that the Office argues that the combination of conditions created by the cited

references would, when combined, teach this element of claims 11 and 25 by inherency. In order to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities (see, MPEP §2112 and In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)). It has been previously shown that the addition of regular amounts of the anticoagulant ACD to blood as disclosed in Bianchi and Simmons, would not create the conditions that cause "the density of said NRBCs to decrease and the cell density of said monocytes and lymphocytes to increase" (see declaration, which will be discussed in some more detail later on). Thus, it has been shown that the missing descriptive matter is not necessarily present in the methods disclosed in the prior art.

Also, in example 10 of Bianchi, the step that the Office continues to argue to produce the conditions that allow (a) "the density of said NRBCs to decrease and the cell density of said monocytes and lymphocytes to increase" and thus (b) the presence of NRBCs in a low density cell fraction after centrifugation, is explicitly disclosed by Binachi to result in a "mononuclear cell layer" (column 22, line 44). This teaching of a "mononuclear cell layer" implies that there is no separation of NRBCs and monocytes/ lymphocytes and thus directly contradicts the Office's inherency argument.[1] There is certainly no suggestion or motivation, either in Bianchi or in the knowledge generally available to one of ordinary skill in the art, to modify Bianchi or to combine it with another reference to arrive at the claimed invention. Thus, another prong of the *prima facie* obviousness analysis is not fulfilled (MPEP §2142).

In fact, for the reasons stated above, Bianchi teaches away from the claimed invention. In particular Bianchi's disclosure would make a person skilled in the art believe that the density of said NRBCs and said monocytes/ lymphocytes are so similar that they are to be "isolated" as part of a single "layer." Applicant respectfully submits that a *prima facie* case of obviousness, which applicant submits has in the present case

[1] Applicant also notes that Bianchi clearly does not teach either explicitly or by inherency that a low density fraction produced in this step contains NRBCs, which can be ascertained in a subsequent step (claim 17).

not been established, may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. In re Geisler, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997) (see MPEP §2144.05).

With regard to claims 1 and 11, the Office appears to argue that while the previously submitted declaration might have established that Bianchi does not teach the pH ranges specified in these claims, that it does not provide evidence related to pH criticality.

As previously mentioned, to establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. In addition, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Finally, there must be a reasonable expectation of success. (MPEP §2142).

Applicant has shown with in the declaration a *prima facie* case has not been established (see, e.g., first prong of the analysis). Applicant is unaware of a requirement that certain or all elements of the claims need to be critical. Applicant respectfully requests that the Office points applicant to any case law that might establish such a requirement.

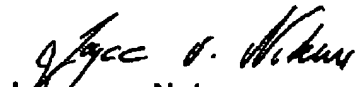
Applicant has shown above that claims 1, 11 and 25 are patentable in view of the cited prior art. Accordingly, these claims should be in condition for allowance. Claim 3 to 6, 8 to 10, 12, 14 to 21 and 25 to 30, which are directly or indirectly dependent thereon, should also be in condition for allowance.

Reconsideration of the application is respectfully requested.

The Examiner is invited to call applicant's representative at the number listed below to further the completion of the prosecution this case.

The Commissioner is authorized to charge any deficiencies in this fee or charge any overpayment to deposit account 50-3135.

Respectfully submitted,



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